In the United States Court of Federal Claims

No. 07-605V
(Originally Filed: June 15, 2015)
(Reissued: July 10, 2015)

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NANCY BARCLAY, as the legal representative of her minor son, MATTHEW RAMIREZ,

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

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Vaccine case; petitioner's challenge to the Special Master's decision; significant aggravation; DTaP vaccine; Dravet syndrome; SCN1A mutation.

Curtis R. Webb, Twin Falls, ID for petitioner.

Voris E. Johnson, Jr., Assistant Director in the Torts Branch of the Civil Division, Department of Justice, Washington, DC, with whom are, *Joyce R. Branda*, Acting Assistant Attorney General, *Rupa Bhattacharyya*, Director, *Vincent J. Matanoski*, Deputy Director, and *Catharine E. Reeves*, Assistant Director, for respondent.

OPINION[1]

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[1] Publication of this opinion was deferred pending the parties' review for redaction of protected information. *See* Rules of the Court of Federal Claims ("RCFC"), App. B, Rule 18(b). Neither party submitted proposed redactions, although the court made other minor editorial changes. The opinion is now prepared for release.

BRUGGINK, Judge.

On August 14, 2007, petitioner, Nancy Barclay, filed a petition for compensation under the National Childhood Vaccine Injury Act, 42 U.S.C. §§ 300aa-1 to-34 (2012) ("Vaccine Act"), on behalf of her minor son, Matthew Ramirez. The petition alleges that the diphtheria-tetanus-acellular pertussis ("DTaP") vaccination caused Matthew to develop Dravet syndrome.[2] Progress on this case was stayed pending the resolution of a series of cases which relied on the same theory of causation. *See Barnette v. Sec'y of Health & Human Servs.*, No. 06-868V, 2012 WL 5285414 (Fed. Cl. Spec. Mstr. Sept. 26, 2012) (denying compensation); *Snyder v. Sec'y of Health & Human Servs.*, No. 07-59V, 2011 WL 3022544 (Fed. Cl. Spec. Mstr. May 27, 2011) (denying compensation); *Harris v. Sec'y of Health & Human Servs.*, No. 07-60V, 2011 WL 2446321 (Fed. Cl. Spec. Mstr. May 27, 2011) (denying compensation); *Hammitt v. Sec'y of Health & Human Servs.*, No. 07-170V, 2011 WL 1135878 (Fed. Cl. Spec. Mstr. Mar. 4, 2011) (denying compensation); *Stone v. Sec'y of Health & Human Servs.*, No. 04-1041V, 2011 WL 836992 (Fed. Cl. Spec. Mstr. Jan. 20, 2011) (denying compensation).[3] Once it became clear that respondent had proven that a genetic factor unrelated to the vaccination was the cause of Dravet syndrome in those cases, Ms. Barclay was permitted to amend her theory of liability.

Petitioner asserts that DTaP vaccine significantly aggravated Matthew's Dravet syndrome by provoking an earlier onset and by causing additional damage to Matthew's brain. Ms. Barclay argues that but for the vaccination, Matthew would have experienced less developmental delay. Petitioner presented her case to the Special Master in June of 2013. After conducting a hearing, reviewing the evidence, weighing the testimony provided by the experts, and considering post-hearing briefs, the Special Master concluded that petitioner failed to establish a persuasive theory of causation, held that respondent proved a defense, and denied petitioner's request for compensation. *See Barclay v. Sec'y of Health & Human Servs.*, No. 07-605V, 2014 WL 7891493 (Fed. Cl. Spec. Mstr. Dec. 15, 2014) (hereinafter "Decision").

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[2] Dravet syndrome is also referred to as SMEI, which stands for severe myoclonic epilepsy in infancy. This condition is characterized by unmanageable epilepsy and developmental regression. *See Stone v. Sec'y of Health & Human Servs.*, 676 F.3d 1373, 1375 n.1 (Fed. Cir. 2012).

[3] *See* footnote 10 for precedent affirming these decisions.

Currently before the court is petitioner's motion for review of the Special Master's ruling of December 15, 2014, denying compensation. We have jurisdiction pursuant to 42 U.S.C. § 300aa-12. In our review, we apply the standard articulated in 42 U.S.C. § 300aa-12(e) and will only set aside the special master's findings of fact or conclusions of law that were "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 42 U.S.C. § 300aa-12(e)(2); *see Paluck v. Sec'y of Health & Human Servs.*, No. 2014-5080, 2015 WL 2403354 (Fed. Cir. May 20, 2015) (precedential); *see also Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1360 (Fed. Cir. 2000) ((holding that special masters have discretion to weigh the evidence and "reversible error is 'extremely difficult to demonstrate'" unless the special master has failed to consider the relevant evidence of record, drawn implausible inferences or failed to articulate a rational basis for the decision) (quoting *Hines v. Sec'y of Health & Human Servs.*, 940 F.2d 1518, 1528 (Fed. Cir. 1999))).

The matter is fully briefed and we heard oral argument on May 7, 2015. For the reasons explained below, we deny petitioner's motion for review.

BACKGROUND[4]

Matthew was born on November 16, 2004. Although he appeared normal and healthy, Matthew was born with a genetic mutation.[5] Specifically, there was a frameshift mutation in his SCN1A gene caused by the "deletion of 10 base pairs at nucleotide position 3867-3876 / codon position 1289-1292." Decision at *5 n.9. Without the missing base pairs, Matthew lacks the necessary genetic material to support proper neurological function.

In a healthy person, the SCN1A gene supplies the genetic code which is used by the body to create $Na_v1.1$ sodium channels.[6] Sodium channels are

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[4] The background facts are derived from the Decision and are not in dispute. The page numbers used in citations to the Decision refer to the pagination provided by Westlaw.

[5] The precise mutation that afflicts Matthew was revealed through genetic testing in 2009.

[6] For more information on transcription and translation, which are the processes by which the body eventually produces the proteins proscribed by

(continued...)

integral to neurological function because they regulate electrical excitability. Specifically, sodium channels transmit electrical signals throughout cells and cell networks to achieve functions such as movement or thought. The transmission is achieved when the membrane of a sodium channel becomes depolarized because it increases permeability to sodium ions and thereby permits the flow of these ions. Once the need for the excitability concludes, permeability decreases and the sodium channel closes.

Within the infant's brain, sodium channels evolve in the first six months of life. At birth, the human body relies on the $Na_v1.3$ sodium channel instead of the $Na_v1.1$ channel. Around three months of age, there is a natural transition to reliance on the $Na_v1.1$ sodium channel. The $Na_v1.1$ sodium channel functions to maintain a neurological balance in the brain and dysfunction in this channel can lead to seizures.

Because Matthew's body was not yet utilizing the $Na_v1.1$ sodium channel, Matthew was asymptomatic during his early development. He had well-baby visits on November 30, 2004, January 21, 2005, and March 25, 2005, during which his pediatrician noted nothing out of the ordinary.

During the March 25, 2005 well-baby checkup, Matthew received a set of vaccinations, which included a second dose of the DTaP vaccine. Later that night, Matthew developed a fever and, in response, Matthew's mother gave him infant Motrin. Around 6:00 a.m. on the morning of March 26, Matthew had a seizure lasting about 20 minutes. Matthew lost consciousness during the seizure, prompting his parents to bring him to the hospital. Upon arriving at the local emergency room, Matthew was still seizing and remained feverish. The doctor administered Versed, and the seizure abated within a minute. Matthew's seizure lasted approximately 45 minutes.

While Matthew was in the hospital, the doctors ordered a series of tests including an electroencephalogram ("EEG"), a computerized tomography ("CT") scan of his brain, magnetic resonance imaging ("MRI"), and X-rays. The EEG and CT scan were normal, and the MRI was essentially normal. The X-ray, however, revealed infiltrate in both lungs. The doctors concluded that Matthew had pneumonia, and his final diagnosis was stated to be febrile seizures due to pneumonia. On March 29, 2005, after being hospitalized for

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[6](...continued)
the DNA, see Decision at *3-4.

four days, Matthew was discharged with a course of antibiotics to treat the pneumonia.

Matthew experienced another seizure on April 15, 2005, although this episode was not provoked by a fever or other identifiable trigger. Shortly after this episode, Matthew had an EEG which "indicated that Matthew had some slowing in the background and was interpreted as abnormal." Decision at *7. After Matthew suffered another unprovoked seizure on April 25, 2005, he fit the criteria for being epileptic.

Matthew continues to suffer from epilepsy. The Special Master summarized Matthew's condition as follows: "Since he started having seizures, Matthew has not developed normally. Various anticonvulsant medicines have not controlled his seizures. He experiences approximately ten seizures each month. He speaks sentences that are three or four words in length. He can walk but has difficulty catching a ball." *Id*.

In 2009, Matthew underwent genetic testing to explore the cause of his epilepsy. The genetic testing report issued by Athena Diagnostic, Inc. stated, "This individual possesses a DNA sequence variant that is either a previously reported disease-associated mutation or is predicted to be a disease-associated mutation. This test result is consistent with a diagnosis of, or a predisposition to develop, SMEI or SMEB, the severe phenotypes associated with SCN1A mutations." *Id*. at * 5 (quotation and citation omitted). Upon receiving these test results, Matthew's treating physicians diagnosed him as suffering from Dravet syndrome.

The presentation of Dravet syndrome includes onset of seizures sometime between four and eight months of age. These initial seizures are typically clonic or hemi-clonic and last for over five minutes or occur multiple times in a five-minute period. "In the second or third year of life, the seizures evolve into different types of seizures including myoclonic seizures, absence seizures, and complex partial seizures. Although the initial development is normal, by the time the child becomes a toddler, his or her development stagnates." *Id*. at *4. The severity of Dravet syndrome occurs along a spectrum with some children experiencing milder outcomes than others. There are subtypes of Dravet syndrome that serve to categorize presentations within the spectrum. These subtypes include "generalized epilepsy with febrile seizures (GEFS), severe myoclonic epilepsy borderline (SMEB), and severe myoclonic epilepsy in infancy (SMEI)." *Id*. As discussed below, the location

and nature of the genetic mutation may be indicative of the child's outcome along the spectrum.

After the test results revealed that Matthew had a severe mutation to his SCN1A gene, his parents were also tested in order to determine if the mutation was hereditary. If one or both of Matthew's parents had a similar mutation that would suggest a more hopeful prognosis for Matthew; the assumption is that the parent with the mutation has developed normally enough to function and reproduce. For example, there are some SCN1A mutations that are associated with conditions such as migraines. These more benign mutations could be inherited. The test results showed that neither of Matthew's parents had a SCN1A gene abnormality.

The alternative to an inherited abnormality is a genetic mutation that occurred spontaneously and for the first time, *de novo*, in Matthew's development. While a *de novo* mutation does not automatically mean a severe outcome, it is not as promising as a hereditary mutation.

Another indicator that the outcome might be severe is location on a conserved region of DNA. A conserved region is one that is preserved through evolution in many species, which suggests that changes in these sequences of DNA are not easily tolerated. Some mutations that occur in conserved regions are not consistent with life.

The type of genetic mutation also impacts outcome. While some types of mutations are harmless, such as when one amino acid is substituted for a similar amino acid, other types, such as frame shift mutations in which base pairs are missing and the DNA sequence shifts in their absence, might be predictive of worse outcomes.

DISCUSSION

To receive compensation for a vaccine related injury, petitioner bears the burden of proving by a preponderance of the evidence the elements of his or her petition, which are listed in 42 U.S.C. § 300aa-11(c)(1). 42 U.S.C. § 300aa-13(a)(1)(A). In a non-table[7] significant aggravation claim, petitioner

[7] *See* 42 U.S.C. § 300aa-14(a) (injury table); *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (explaining that "[i]n a (continued...)

must prove that he or she "had significantly aggravated any illness, disability, injury, or condition not set forth in the Vaccine Injury Table but which was caused by a vaccine." § 300aa-11(c)(1)(C)(ii)(I). "Significant aggravation" is defined in § 300aa-33(4) as "any change for the worse in a preexisting condition which results in a markedly greater disability, pain, or illness accompanied by a substantial deterioration of health."

A critical step in petitioner proving her case is showing that the vaccine caused the significant aggravation. The Court of Appeals for the Federal Circuit in *W.C. v. Secretary of Health and Human Services*, 704 F.3d at 1357, endorsed the factors for establishing causation in a significant aggravation case set forth in *Loving v. Secretary of Health and Human Services*, 86 Fed. Cl. 135 (2009). The *Loving* case suggests an examination of the following factors:

> (1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a "significant aggravation" of the person's condition prior to vaccination, (4) a medical theory casually connecting such a significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) . . . a proximate temporal relationship between the vaccination and the significant aggravation.

86 Fed. Cl. at 144.[8] Additionally, petitioner must show that "the residual effects or complications of such illness, disability, injury, or condition"

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[7](...continued)
table claim, the petitioner benefits from a statutory presumption of causation upon showing that the injury is listed in the Vaccine Injury Table for the vaccine received and occurred within the time period in the table" but that "[i]f the injury is not listed in the table, the petitioner must prove actual causation by a preponderance of the evidence").

[8] The *Loving* standard combines the traditional causation factors outlined in *Althen v. Secretary of Health and Human Services*, 418 F.3d 1274, 1278 (Fed. Cir. 2005), with three additional factors for establishing an off-table significant aggravation claim derived from *Whitecotton v. Secretary of Health and Human Services*, 81 F.3d 1099, 1107 (Fed. Cir. 1996).

continued "for more than 6 months after the administration of the vaccine." § 300aa-11(c)(1)(D)(i). If petitioner proves these factors, she has established a prima facie case for compensation.

At any point, whether it is before or after petitioner has established her prima facie case, the Special Master may consider whether a factor unrelated to the vaccine was the cause of the injury. *Stone*, 676 F.3d at 1379-80. The Secretary bears the burden of proving the "factors unrelated" defense, which requires a showing "also by a preponderance of evidence, that the injury was in fact caused by factors unrelated to the vaccine." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 547 (Fed. Cir. 1994) (citation and quotation omitted).

The anomaly in using this approach here, however, is that Matthew had a preexisting condition which had not manifested itself prior to the vaccination. Asking the question, "what was Matthew's condition prior to the vaccination?" therefore, requires addressing the issue of his genetic abnormality. Does the fact that the abnormality had not manifested and was therefore unknown mean that his condition prior to vaccination was that of a normal, healthy child? The result of the before and after comparison posed by questions one and two in the *Loving* analysis is different depending on whether or how the genetic abnormality is taken into account.

Petitioner does not contend that the vaccine caused the Dravet syndrome. In other words, she concedes that Matthew's "before" condition is that of a child with a genetic abnormality, which, as we consider below, means that he will develop one of the severe disease types associated with SCN1A mutations. She contends, however, that the vaccination triggered the earlier onset of the manifestations of Dravet and that those symptoms were, on a continuing basis, more serious than they otherwise would have been.

Further complicating the application of the *Loving* factors, however, is that it is undisputed that the vaccine caused the fever which preceded the seizure on the day of vaccination. There is thus no question that Matthew's condition immediately prior to vaccination was that he was free of fever and seizures, and that after the vaccination he had a fever (briefly), but continued to have seizures. Under these circumstances, determining whether or not the causation test is met depends on how the question is framed. Is it sufficient that there is a connection between the vaccination and the first seizure, or must the first seizure have had an impact on Matthew's ultimate prognosis? What specific condition must have persisted at least six months to establish

causation, and what must petitioner prove, if anything, with respect to whether the genetic abnormality alone explains the ongoing seizures?

I. Before the Special Master

A. The Parties' Arguments and Experts

Before the Special Master, petitioner presented three overlapping theories of causation. First, that individuals "with an SCN1A mutation are vulnerable or susceptible to developing an adverse reaction to the DTaP vaccine." Decision at *12. Second, that "vaccines cause Dravet syndrome to manifest earlier by bringing about seizures before they would have occurred otherwise." *Id*. Third, that "vaccines cause a more prolonged seizure and the prolonged seizure inflicts additional damage." *Id*.

In order to establish its prima facie case, petitioner relied on the expert opinion of Jean-Ronel Corbier, a pediatric neurologist. Dr. Corbier offered his medical opinion that "a prolonged seizure, especially a prolonged febrile seizure, can change the infant's brain" and thereby significantly aggravate a preexisting condition such as a SCN1A genetic mutation. *Id*. at *9. Specifically, Dr. Corbier testified that a person with a SCN1A mutation could potentially experience a range of outcomes from benign migraines to much more severe conditions. He opined that the broad spectrum of disorders was not explained solely by genetics and was likely caused to some extent by environmental factors. In Matthew's case, Dr. Corbier testified that the second dose of the DTaP vaccine was an environmental factor that caused a fever and a prolonged febrile seizure, which damaged Matthew's brain and significantly aggravated his ultimate outcome. While Dr. Corbier acknowledged that Matthew's EEG and MRI test results were normal shortly after receiving the second dose of DTaP, he asserted that the March 26, 2005 seizure altered Matthew's brain. "In Dr. Corbier's view, 'an immature brain exposed to prolonged febrile seizure will then not have just an isolated event but will have further seizures.'" *Id*. at *8 (quoting Tr. 99). Dr. Corbier conceded that Matthew was at risk for epileptic conditions because of his SCN1A mutation, but asserted that the vaccine triggered an earlier onset of epilepsy, which damaged Matthew's brain and altered his outcome for the worse.

Dr. Corbier drew support for his opinion from scientific material related to SCN1A mutations. Specifically, Dr. Corbier relied on the Tro-Baumann study for the proposition that there is a connection between vaccination and Dravet syndrome. *See* Blanca Tro-Baumann et al., *A Retrospective Rtudy of*

the Relation Between Vaccination and Occurrence of Seizures in Dravet Syndrome, 52 Epilepsia 175 (2011). Tro-Baumann and colleagues studied 70 patients with Dravet syndrome and SCN1A mutations and noted that 27% of them experienced seizures after vaccination. In more than half of the patients who reported a seizure following vaccination, it was their first clinical manifestation of Dravet syndrome. While the authors of the study concluded that drawing a causal connection between vaccination and onset of Dravet syndrome would be a misinterpretation of the data, Dr. Corbier presented this study as support for his opinion that vaccination is an inciting factor that could trigger early disease onset in genetically susceptible individuals like Matthew.

Dr. Corbier's theory that vaccines cause a more prolonged seizure and that the prolonged seizure inflicts additional damage was based on medical studies which examined whether febrile seizures damage HCN channels. Dr. Corbier testified that "'these articles show that we have an explanation for prolonged febrile seizures causing permanent changes, permanent epileptic changes in a brain that may start out normal, for example, Dravet patients.'" Decision at *18 (quoting Tr. 50). Dr. Corbier testified that Matthew had suffered some sort of alteration to his brain during his initial seizure, even though he could not point to any medical evidence showing the alleged damage and despite the fact that the neurological tests performed directly after Matthew's initial epileptic episode yielded normal results.

Respondent's position is that Matthew's genetic mutation is a factor unrelated to the vaccine and that the mutation is the sole cause of his present condition. The Secretary is willing to concede that the vaccination caused a fever, and that the fever may have triggered a seizure, but whether the seizures started immediately upon the vaccination or later, she argues that Matthew's outcome is the same as it would have been absent the vaccination. Respondent relies on two experts: Max Wiznitzer, a pediatric neurologist, and Gerald Raymond, a neurologist and geneticist. Both experts supported the Secretary's position that the vaccine neither caused nor significantly aggravated Matthew's Dravet syndrome. Dr. Wiznitzer testified about the course of Matthew's condition and Dr. Raymond supplied information about the interplay between Matthew's genetic mutation and the function of sodium channels. Both respondent experts agreed with Dr. Corbier only to the extent that the vaccination most likely provoked a fever that triggered the first seizure.

Dr. Wiznitzer was of the opinion that Matthew's SMEI condition was caused solely by the mutation in his SCN1A gene. He asserted that there is no

medical or scientific evidence that environmental factors can aggravate a SCN1A gene mutation. To the contrary, the Secretary presented a medical study conducted by Yu and his colleagues. *See* Frank H. Yu et al., *Reduced Sodium Current in GABAergic Interneurons in a Mouse Model of Severe Myoclonic Epilepsy in Infancy*, 9 Nat. Neuroscience 1142 (2006). It showed how mice with a severe SCN1A mutation were destined to develop seizures even in the absence of a fever or other triggering event. In light of this study and his medical experience, Dr. Wiznitzer concluded that "the initial post-vaccination fever did not affect Matthew's development because children with SMEI always manifest the disorder even if they do not have a fever." Decision at *8 (citation and internal quotation omitted). Dr. Wiznitzer also relied on the McIntosh study, which examined 40 patients with Dravet syndrome to see if there was an association between vaccination and disease onset. *See* Anne M. McIntosh et al., *Effects on Vaccination on Onset and Outcome of Dravet Syndrome: A Retrospective Study*, 9 Lancet Neurology 592 (2010). The study concluded that there were "no differences in intellectual outcome, subsequent seizure type, or mutation type between" those whose disease manifested directly following vaccination and those whose disease manifested later. *Id.* at 592. Additionally, McIntosh and her colleagues found "no evidence that vaccinations before or after disease onset affect outcome." *Id.*

Dr. Wiznitzer opined that McIntosh suggests that children with Dravet syndrome who have an initial seizure in temporal proximity to a vaccination still have similar clinical outcomes to children whose initial seizures are not temporally related to vaccination. Furthermore, Dr. Wiznitzer saw no evidence that Matthew's brain had been affected by the March 26, 2005 seizure. Dr. Wiznitzer was therefore of the opinion that Matthew returned to baseline and had no readily identifiable lasting effects from the March 26 episode. Dr. Wizniter opined that Matthew's faulty "wiring" and not the vaccine caused his present condition.

Dr. Wiznitzer also addressed Dr. Corbier's testimony that the medical literature supported his conclusion that prolonged febrile seizures had damaged Matthew's brain. First, Dr. Wiznitzer pointed out that HCN channels are not the same as sodium channels, with the latter and not the former being altered by the SCN1A mutation. Dr. Wiznitzer explained that HCN channels are located in the hippocampal region of the brain and exist to limit the cell's excitability through the movement of sodium and potassium ions across the cell membrane. The exchange of sodium and potassium ions balances and polarizes the cell. Sodium channels, by contrast, only regulate the flow of sodium ions. When sodium ions are present, the cell becomes hyper-polarized.

According to Dr. Wiznitzer, the two types of channels are prescribed by different genes, built differently, and have different components. Dr. Wiznitzer was not comfortable extrapolating the medical studies regarding HCN channels to sodium channels.

Respondent's second expert, Dr. Raymond, explained how sodium channels normally function and how a genetic defect can alter their proper functioning. According to Dr. Raymond, the dysfunction of sodium channels was sufficient to explain Matthew's outcome, and "it is very clear that based on the present animal investigations, that there is no need to invoke environmental modifiers to explain disease onset or progression." Decision at *10 (internal quotations omitted).

Additionally, Dr. Raymond challenged Dr. Corbier's assertion that an earlier onset of Dravet syndrome caused a worse outcome by pointing to medical studies supporting an opposite conclusion. The Berkovic group studied 14 patients who experienced their first seizure within 72 hours of receiving the pertussis vaccination and thereafter suffered an alleged encephalopathy and found that 11 of those patients had an SCN1A mutation. Samuel F. Berkovic et al., *De-novo Mutations of the Sodium Channel Gene SCN1A in Alleged Vaccine Encephalopathy: A Retrospective Study*, 5 Lancet Neurology 488 (2006). Eight of those 11 patients had severe phenotypes of the SCN1A mutation, which correlates to SMEI. Another 3 patients had an SCN1A mutation that was linked to borderline SMEI. This led the researchers to conclude that genetics, rather than the vaccine, caused the epileptic encephalopathy. Berkovic wrote that "individuals with such mutations seem to develop SMEI or SMEB whether or not they are immunized in the first year of life. We do not think that avoiding vaccination, as a potential trigger, would prevent onset of this devastating disorder in patients who already harbour the SCN1A mutation." *Id*. at 491. Additionally, Dr. Raymond relied on the study conducted by Brunklaus, which tracked 355 SCN1A mutation-positive patients with Dravet syndrome over 5 years to gather data on disease presentation and manifestation. A. Brunklaus et al., *Prognostic, Clinical and Demographic Features in SCN1A Mutation-positive Dravet Syndrome*, 135 Brain 2329 (2012). The authors found that the following variables predicted a worse outcome: "status epilepticus, interictal electroencephalography abnormalities in the first year of life, and motor disorders." Decision at *16. By contrast, variables such as mutation class and the event precipitating seizure did not correlate to a worse outcome. The authors concluded that developmental outcome was not affected by vaccination.

Dr. Raymond also testified about the location, type, and severity of Matthew's mutation. Specifically, Dr. Raymond drew on his experience as a geneticist and explained that the following factors would lead him to expect that Matthew's condition would be severe, irrespective of the vaccination: the fact that the mutation arose *de novo*; that Matthew's mutation was the deletion of ten base pairs of nucleotides; and that the mutation arose in a conserved region. Dr. Raymond's analysis about the significance of Matthew's genetic mutation is consistent with the laboratory that provided Matthew's genetic screening, which concluded that the mutation was indicative of a severe manifestation of SMEI.

B. The Special Master's Decision

In his decision, the Special Master did not perform an analysis as to each of the *Loving* factors. Of the six *Loving* factors, the Special Master focused his analysis on the fourth factor, which corresponds to the first prong of *Althen*.[9] The question asked by the fourth *Loving* factor is whether petitioner has proven "a medical theory causally connecting such a significantly worsened condition to the vaccination." 86 Fed. Cl. at 144. The Special Master was not persuaded by petitioner's theory that the vaccination aggravated the symptoms of the SCN1A mutation, and he accepted respondent's argument that Matthew's presentation of Dravet syndrome is completely explained by his genetic mutation.

The Special Master thus accepted respondent's proof of two things, either of which would be inconsistent with a recovery: that the vaccination did not cause any brain damage making the onset of Dravet more serious; and that the manifestation of the SCN1A mutation would not have been any different if the vaccine had not been administered. The first finding is inconsistent with petitioner's case in chief. The second accepts respondent's defense.

The Special Master considered the parties' arguments and the expert's presentations and concluded that the opinions of respondent's experts were more persuasive than the expert opinion furnished by petitioner: "Dr. Wiznitzer and Dr. Raymond explained the relevant medical concepts and showed how those principles were the foundations for their opinions," while "Dr. Corbier did not." Decision at *1. The Special Master summarized his conclusion regarding the weight of the evidence as follows:

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[9] 418 F.3d at 1278.

> Thus, there is no reliable basis for crediting Dr. Corbier's first theory that people with an SCN1A mutation are vulnerable to developing an adverse reaction to the DTaP vaccine. Similarly, there is no reliable basis for crediting Dr. Corbier's second theory that vaccines worsen Dravet syndrome by bringing about seizures before they would have occurred otherwise. Although there may be an earlier manifestation, Dr. Corbier has not demonstrated how it affects the child's outcome. Dr. Raymond and Dr. Wiznitzer rested their opinion on Berkovic, McIntosh, and Brunklaus. Dr. Corbier, on the other hand, had no support for his opinions that the vaccines change the outcome. These studies showed that children with SCN1A mutations have consistent symptoms, regardless of whether the initial seizure followed a [vaccine].

Id. at *17 (citations omitted). Without a medical theory causally connecting the significant aggravation of Matthew's condition to the vaccine, the Special Master concluded that petitioner had not carried her burden. On the other hand, the Special Master found that respondent had proved by a preponderance of the evidence that a factor unrelated, Matthew's SCN1A mutation, was the sole cause of his present condition. The Special Master considered the age at which the body switches from reliance on the $Na_v1.3$ channel to the $Na_v1.1$ channel and found that it was consistent with Matthew's onset.

The Special Master also held that petitioner had not established that, but for the vaccine, Matthew's outcome would not be as severe. According to the Special Master, Dr. Corbier was unable to provide any meaningful information about how Matthew's present condition was different than a typical presentation of Dravet syndrome. Instead, the Special Master found respondent's expert testimony that vaccination does not affect Dravet syndrome to be more persuasive.

Although the aforementioned rationales were sufficient for denying compensation, the Special Master went on to evaluate whether petitioner had established the severity requirement. All of the experts agreed that the vaccine caused Matthew's fever, which triggered the initial seizure. The Special Master noted, however, that following this initial episode Matthew's tests results were normal and upon discharge from the hospital, Matthew was in good condition. According to the Special Master, the effects of this initial fever and isolated seizure did not continue for more than six months. Instead,

the disease that Matthew continues to experience was caused by his genetic mutation.

II. On Review

As we suggested earlier, the *Loving* analysis may not be an ideal fit in dealing with a child who has a genetic mutation that is asymptomatic prior to vaccination. It is not entirely clear from the Special Master's analysis what conclusions he came to with respect to the first three *Loving* factors: "(1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), [and] (3) whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination." 86 Fed. Cl. at 144. Dealing with the fourth factor whether petitioner has proved a causal connection between the aggravation and the vaccination would seem to assume that petitioner has established an after condition that is a significant aggravation of the before condition. Although the outcome in this case is the same, we are not persuaded that petitioner has proved that Matthew's current condition is a significant aggravation of his prior condition, if that prior condition assumes a genetic anomaly which will manifest in Dravet syndrome.

We sympathize with the challenge to the parties and Special Master in dealing with the present tragic circumstances. For her part, petitioner concedes, as she must, that in his condition before vaccination, Matthew had a genetic defect, although he appeared asymptomatic at the time. The Special Master concluded, based on sound medical evidence, that this fact meant that Matthew would develop Dravet syndrome.

Respondent, for its part, concedes that before the vaccine Matthew did not have seizures, but that after the vaccination, he quickly developed a fever and a seizure which can be causally linked to the vaccination. It is also undisputed that Matthew continued to have seizures. From this, petitioner asserts that Matthew's preexisting genetic condition was significantly aggravated because he experienced a change for the worse on March 26, 2005, when Matthew "change[d] from a child who did not have seizures to a child who has frequent seizures." Mot. for Review at 7.

Characterizing Matthew's condition before and after as petitioner proposes would appear to suggest a significant aggravation. The problem for petitioner, however, is that implicit in Matthew's before condition is the genetic anomaly which, as a practical matter, undisputedly will lead to

continuing seizures. The subsequent seizures and development of Dravet syndrome, given the findings on the lack of connection to the vaccination, cannot be attributed to the vaccine. In sum, if we view the significant aggravation as the ongoing seizures, Matthew's condition prior to vaccination included the genetic abnormality and the inevitable Dravet syndrome. There is thus no significant aggravation *and* no causal connection.[10]

If we view the initial fever and seizure as the aggravation, there is a causal connection but no significance to the aggravation. The seizure was short-lived. Matthew had recovered from this episode within a few days, and the injury is thus not severe under § 300aa-11(c)(1)(D)(i). The causal connection between the vaccination and the initial fever, in other words, is insufficient to establish liability.

Petitioner's best hope for establishing liability was to attempt to prove that Matthew's before condition was that of a child who would ultimately develop seizures, but who, after the vaccination, is a child whose seizures and developmental delay are more severe because of the vaccine. We have reviewed the Special Master's careful analysis of the evidence about this connection and find no basis for overturning his finding that petitioner did not demonstrate a causal connection between the vaccine and a heightened severity of symptoms. He found Drs. Wiznitzer and Raymond's evidence more persuasive than that of Dr. Corbier. We find no basis for overturning his analysis.

Petitioner also argues that the Special Master elevated her burden of proof by requiring her to establish that the vaccine affected Matthew's ultimate outcome. Petitioner is correct that it is not her burden to prove what Matthew's ultimate prognosis would have been, but for the vaccination. Indeed, even if the ultimate prognosis were the same with and without the

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[10] There have been numerous prior determinations that the SCN1A mutation was the sole cause of the child's Dravet syndrome. *See, e.g., Stone/Hammitt v. Sec'y of Health & Human Servs.*, 676 F.3d 1373 (Fed. Cir. 2012), *reh'g en banc denied* 690 F.3d 1380, *cert. denied sub nom. Stone v. Sebelius*, 133 S.Ct. 2022 (Apr. 29, 2013); *Deribeaux v. Sec'y of Health & Human Servs.*, 717 F.3d 1363 (Fed. Cir. 2013); *Snyder/Harris v. Sec'y of Health & Human Servs.*, 553 Fed. App'x 994 (Fed. Cir. 2014); *Barnette v. Sec'y of Health & Human Servs.*, 110 Fed. Cl. 34 (2013).

vaccination, there would still be room, presumably, to argue that for at least six months the child's condition was significantly worse than it would have been without the vaccination. We view the Special Master's statements concerning ultimate outcome, however, in the context of respondent's theory of alternative causation. In the circumstances of this case, the "ultimate" outcome and the significant aggravation petitioner attempted to prove were one and the same and neither can be attributed to the vaccination.

CONCLUSION

Because the Special Master's decision was in accordance with the law, and was not otherwise arbitrary or capricious, we affirm. For the reasons set forth above, we deny petitioner's motion for review. The clerk is directed to enter judgment accordingly. No costs.

s/Eric G. Bruggink
ERIC G. BRUGGINK
Judge